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Administration of Lispro Insulin with Meals Improves Glycemic Control, Increases Circulating Leptin, and Suppresses Ghrelin, Compared with Regular/NPH Insulin in Female Patients with Type 1 Diabetes

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Context: Overweight and obesity are overrepresented in adolescents with type 1 diabetes mellitus (T1DM). Exogenous insulin administration often poorly reproduces normal insulin patterns and may less effectively regulate leptin and ghrelin, two hormones involved in the control of appetite and adiposity.

Objective: The objective of the study was to determine whether insulin regimens that better replicate normal insulin patterns and augment postprandial nutrient disposal may help normalize leptin and ghrelin and improve body weight regulation.

Design, Setting, and Participants: Ten young women with T1DM were studied in this 2-wk prospective, balanced crossover-design study at the University of California, Davis.

Intervention: Participants received either a single injection of regular + NPH insulin (R+N) or two mealtime injections of Lispro insulin in randomized order on 2 separate days. Meal composition and total insulin administered were the same on both treatment days.

Main Outcome Measures: Plasma glucose, insulin, leptin, and ghrelin concentrations were monitored over the 10-h study period.

Results: Lispro produced two distinct mealtime peaks of insulin, compared with one prolonged rise with R+N. Lispro reduced postprandial hyperglycemia and total glucose area under the curve. Leptin increased more on the Lispro (2.7 ± 0.7 *vs.* 0.7 ± 0.5 ng/ml, $P = 0.02$). Ghrelin was more suppressed after lunch with Lispro ($P = 0.004$).

Conclusions: Injection of Lispro insulin with meals produces more physiological insulin patterns, better glucose control, and improved leptin and ghrelin regulation than R+N. More closely mimicking normal insulin, leptin, and ghrelin responses to meals with fast-acting insulin may have implications for body weight regulation in T1DM. **(*J Clin Endocrinol Metab* 91: 485–491, 2006)**

YOUNG INDIVIDUALS WITH type 1 diabetes mellitus (T1DM), particularly adolescent females, have an increased prevalence of overweight and obesity (1–3), placing them at greater risk for metabolic complications. This observation is somewhat surprising given that these patients are susceptible to severe catabolic states when insufficient insulin is administered. Excess weight in patients with T1DM is associated with both twice-daily and multiple-daily injection insulin regimens as well as less rigorous adherence to dietary recommendations (2–4). In the short term, rapid improvement of glycemic control is often associated with weight gain, as was seen in the first year of the Diabetes Control and Complications trial (5). This has commonly attributed to a variety of factors, including a reduction in catabolism, diminished caloric loss from glucosuria, and increased energy intake triggered by more frequent episodes of hypoglycemia that can occur with more intensive therapy. However, reports are conflicting with regard to the association of metabolic control or total insulin dose and long-term weight control (1, 5, 6), leaving the underlying cause for increased overweight/obesity in T1DM unresolved. One potential explanation is that the endocrine systems involved in regulation of appetite and body weight may be dysfunctional in T1DM. A vast array of hormonal and neural signaling pathways control food intake and energy expenditure, and insulin is implicated in this process at multiple levels (7, 8).

Insulin regulates, at least in part, the hormones leptin and ghrelin. Leptin and ghrelin are two key factors in the control of energy balance (9, 10), and therefore, a lack of normal physiological regulation of these endocrine signals may have a role in overweight and obesity in T1DM. Leptin is produced by adipocytes in proportion to adipose tissue mass and recent energy intake. It serves as a signal of long-term energy status to the brain, acting to decrease food intake and enhance energy expenditure (11). Ghrelin is an acylated peptide secreted from endocrine cells in the stomach and upper intestine (12, 13). Ghrelin's actions on energy balance are opposite to those of leptin, and ghrelin activates rather than inhibits hypothalamic neuropeptide

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Abbreviations: AUC, Area under the curve; BMI, body mass index; Δ[Leptin], change of leptin; R+N, regular + NPH insulin; T1DM, type 1 diabetes mellitus.

Y/agouti gene-related peptide signaling (14). Ghrelin enhances appetite and increases food intake (15). In concert, leptin and ghrelin serve as vital regulators of energy homeostasis.

Based on the evidence that insulin, glucose, and glucose metabolism are involved in the regulation of leptin and ghrelin, we hypothesized that alterations in normal postprandial insulin excursions (and therefore nutrient disposal) might result in dysfunctional regulation of the postprandial stimulation of leptin production and suppression of ghrelin secretion. In the long term, this dysregulation could contribute to abnormal weight gain and overweight/obesity in patients with T1DM.

Many patients with T1DM are managed with conventional insulin therapy, using twice-daily injections of a mixture of fast-acting and intermediate-acting insulin preparations, often regular and neutral protamine Hagedorn (NPH). The pattern of circulating insulin levels with this type of regimen is markedly different from that in nondiabetic individuals, in whom insulin levels increase rapidly and then quickly decline after each meal. Newer, more rapid-acting and shorter-acting insulin analogs make it possible to more closely reproduce the normal insulin responses to meals. We sought to determine whether two injections of rapid-acting Lispro insulin before breakfast and lunch would result in enhanced leptin production and more pronounced postprandial suppression of ghrelin, compared with a more conventional regimen of a single morning injection of the same total number of units of regular and NPH (R+N) in patients with T1DM. Insulin regimens that better replicate normal postprandial insulin responses could enhance the endocrine regulation of energy balance and reduce the predisposition to overweight and obesity. These results would have important therapeutic implications for the treatment of patients with T1DM.

Subjects and Methods

Subjects and subject selection

Twelve female subjects with T1DM [Tanner stage V: age 14–32 yr, body mass index (BMI) 24.5 ± 1.9 kg/m^2, range 17–35 kg/m^2, percent body fat 30 ± 3%] were recruited from the Pediatric and Young Adult Diabetes Clinics of the University of California, Davis, Medical Center and advertisements on the University of California, Davis campus. Only individuals currently using Lispro insulin were included in the study. Most patients were using continuous sc insulin infusion via insulin pumps. Subjects using a combination of Lispro and NPH insulin were included only if their evening insulin was taken before 1700 h (n = 2) to eliminate potential effects of residually acting NPH insulin. Subjects with chronic diseases other than diabetes were excluded.

Only female subjects were included in the study because young female patients with T1DM have a higher prevalence of overweight/obesity than males. In addition, women have higher circulating plasma leptin concentrations and larger leptin responses to meal-induced insulin secretion than men (16, 17). Therefore, changes of circulating leptin in response to differing insulin regimens would be more readily detectable in female subjects. The Institutional Review Board of University of California, Davis approved the experimental protocol, and subjects provided informed consent to participate in the study.

Experimental protocol

The study was a balanced crossover design in which patients were studied on 2 randomized experimental days, approximately 1 wk apart. On 1 study day, subjects received the conventional insulin treatment (R+N). On the other study day, subjects received Lispro insulin with each of the two meals served. The conventional treatment consisted of a single sc injection of premixed NPH and regular recombinant human insulin (Humulin 70/30; Eli Lilly, Indianapolis, IN) self-administered in the abdominal region before breakfast (0900 h). On the Lispro treatment day the subjects administered two injections of Lispro insulin (Eli Lilly) of equivalent dosage, one with breakfast and one with lunch. The insulin dose was calculated according to each individual subject's usual regimen and was determined by multiplying the patient's prescribed ratio of Lispro insulin to carbohydrate (units insulin per gram carbohydrate) by the grams of carbohydrate in the meals provided. The total amount of insulin administered did not differ between the R+N (26.3 ± 3.7 U) and the Lispro treatment days (26.0 ± 3.7 U).

The meals were designed to provide appropriate caloric intake for each individual based on maintenance energy requirements, with equal amounts of carbohydrates and total calories at breakfast and lunch. The meals consisted of whole foods providing 60% of energy as carbohydrate, 20% as fat, and 20% as protein. The same meals were fed on each study day. After an overnight fast, subjects arrived at the Pediatric Infusion Center between 0715 and 0730 h to begin the protocol. Subjects using insulin pumps were instructed to turn the pump off at 0700 h. Subjects using a combination of Lispro and NPH insulin were instructed to inject NPH insulin at the same time in the evening before each of the 2 study days (before 1700 h).

Body weight and height were determined on arrival to the Infusion Center. Body composition was determined by bioelectrical impedance analysis (Bodystat, Isle of Man, UK). An iv catheter was placed in an arm vein and kept patent by the slow infusion of 0.9% normal saline throughout the study. Blood sampling began at 0800 h, and samples were taken every 30 min for 10 h, except for 1 h after each meal, during which samples were taken at 15-min intervals to define better the postprandial insulin and glucose concentrations. The subjects were given breakfast at 0900 h and lunch at 1300 h. Subjects were permitted free access to water. Blood glucose was monitored at bedside throughout the day with a glucometer to ensure subjects did not become hypoglycemic.

Biochemical analyses

Plasma glucose was determined with a YSI glucose analyzer (Yellow Springs Instruments, Yellow Springs, OH). Plasma leptin was measured using a RIA kit from Linco Research, Inc. (St. Charles, MO). Insulin was measured using RIA as previously described (18) with insulin tracer purchased from Amersham Biosciences (Piscataway, NJ) and antibody purchased from RadioAssay System Laboratories (Carson, CA). This antibody is fully cross-reactive with Lispro, NPH, and regular insulin. All samples from each subject were run within the same assay. Total immunoreactive ghrelin was determined with our modification of a commercial RIA (Phoenix Pharmaceuticals, Belmont, CA). This assay uses a 125-I-labeled ghrelin tracer and a rabbit polyclonal antibody against full-length, octanoylated human ghrelin that recognizes the acylated and des-acyl forms. Although only acylated ghrelin is bioactive (13), total ghrelin appears to be a reasonable surrogate for the acylated form because the ratio of the two levels remains constant under a wide variety of conditions that affect ghrelin (19, 20). The lower and upper detection limits were 80 and 2500 pg/ml, respectively, and the inter- and intraassay coefficients of variation were 5.9 and 10.3%, respectively.

Calculations and statistical analysis

Twelve female subjects participated in the study. Data from two subjects were not included because the difference in day-long circulating insulin concentrations between the 2 treatment days was greater than 45%. The difference likely resulted from poor insulin injection technique leading to impaired insulin absorption on 1 study day. The data presented are from the 10 subjects in which the mean insulin concentration differed by less than 25% between the 2 study days.

Total leptin responses were determined by calculating the integrated leptin area-over-nadir levels [area under the curve (AUC)]. This is done by subtracting the mean nadir value (average of three lowest consecutive morning samples) and calculating the AUC over 10 h using the trapezoidal method, as previously described (21). The integrated ghrelin response to meals was determined by calculating the area under premeal nadir levels (AUC). The total AUC above baseline levels for both insulin

and glucose was also calculated. Paired *t* tests were performed and significance was set at $P < 0.05$. Results are presented as mean ± SEM.

Results

Insulin

As expected, the pattern of circulating insulin concentrations differed markedly between the two insulin regimens (Fig. 1A). Plasma insulin levels increased similarly after breakfast; however, after Lispro injection, insulin levels increased rapidly and returned close to baseline levels before lunch. There was a second insulin peak of similar magnitude after Lispro administration with lunch, and values declined to below baseline within 4 h. After R+N administration, insulin levels increased gradually, peaked at 1100 h, and then declined slowly throughout the remainder of the study period. The total insulin AUC did not differ between treatment days ($P = 0.44$; Fig. 1B). This was expected because subjects received the same total number of units of insulin on each treatment day.

Glucose

Baseline plasma glucose concentrations tended to be lower on the Lispro treatment day, but the difference was not statistically significant ($P = 0.06$, Fig. 2A). Postprandial glucose levels were lower on the Lispro treatment day and the difference was most pronounced during the 2–3 h after breakfast and lunch. The total glucose AUC was approximately 60% lower on the Lispro treatment day, compared with the R+N treatment day ($P = 0.024$, Fig. 2B). This finding indicates significantly improved glycemic control and glucose disposal with Lispro, compared with conventional R+N treatment, even though the total calories and amount of carbohydrate ingested and the number units of insulin received were equivalent in both conditions.

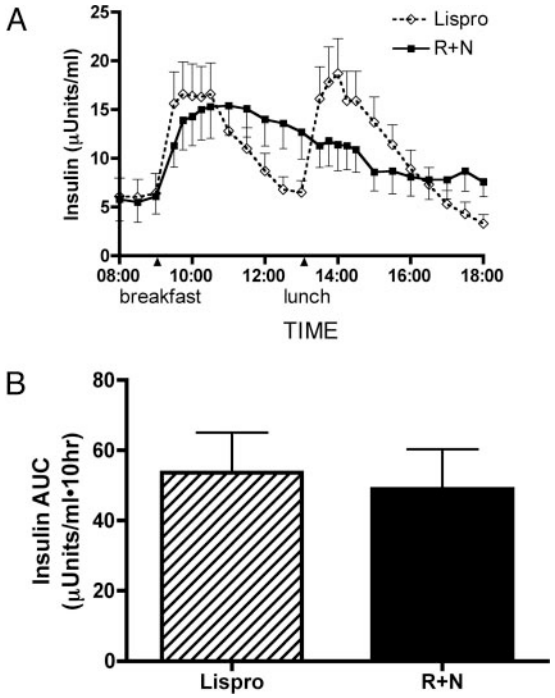

FIG. 1. A, Plasma insulin concentrations over a 10-h period (0800–1800 h) in 10 female subjects with T1DM receiving Lispro insulin with breakfast and lunch or R+N with breakfast. Identical meals were consumed and the same total number of units of insulin was given on each study day. B, The AUC for plasma insulin concentrations above baseline levels over 9 h after breakfast in 10 female subjects with T1DM receiving Lispro insulin or R+N.

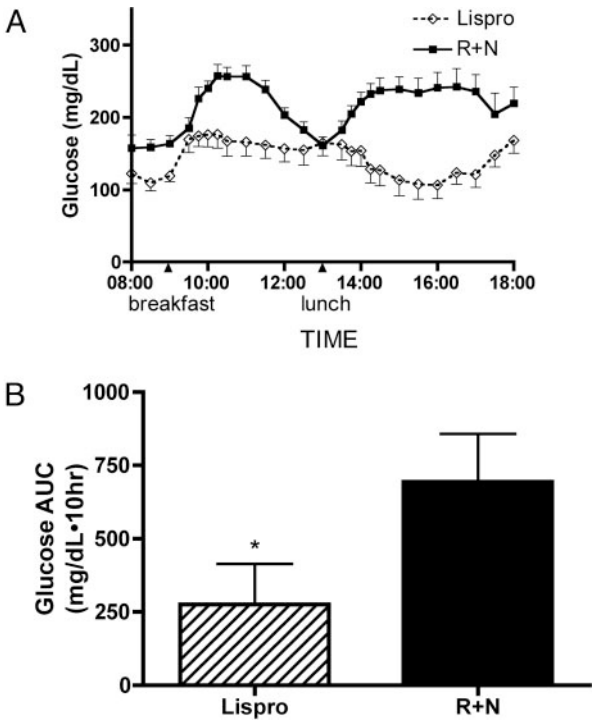

FIG. 2. A, Plasma glucose concentrations over a 10-h period (0800–1800 h) in 10 female subjects with T1DM receiving Lispro insulin or R+N. B, The AUC for plasma glucose concentrations above baseline levels over 9 h in 10 female subjects with T1DM receiving Lispro insulin or R+N. *, $P = 0.024$ for Lispro treatment, compared with R+N.

Leptin

Baseline fasting plasma leptin concentrations tended to be somewhat higher in these young women with T1DM than those reported in a group of nondiabetic women with a similar mean BMI and body adiposity (BMI 23.4 ± 0.46 kg/m^2, body fat 27.4 ± 1.12%) (17). Mean baseline leptin concentrations were not different on the 2 treatment days; however, leptin levels varied widely between subjects, ranging from 3 to 46 ng/ml. Due to this variability, the change of leptin (Δ[Leptin]; Fig. 3A) from the morning nadir was calculated, as previously described (21). This method allows direct comparison of subjects with differing baseline adiposity and leptin levels, and the Δ[Leptin] has been implicated as an important regulator of central energy homeostasis (21).

The early patterns of circulating leptin were similar after each of the insulin treatments, with morning nadir levels occurring at about 1000–1100 h, as previously reported in nondiabetic subjects (21). On the Lispro study day, plasma leptin increased approximately 4 ng/ml above nadir levels by 1700 h. On the R+N regimen, the increase of leptin was consistently lower, with mean Δ[Leptin] less than 1 ng/ml for all but three time points. After lunch, when differences in

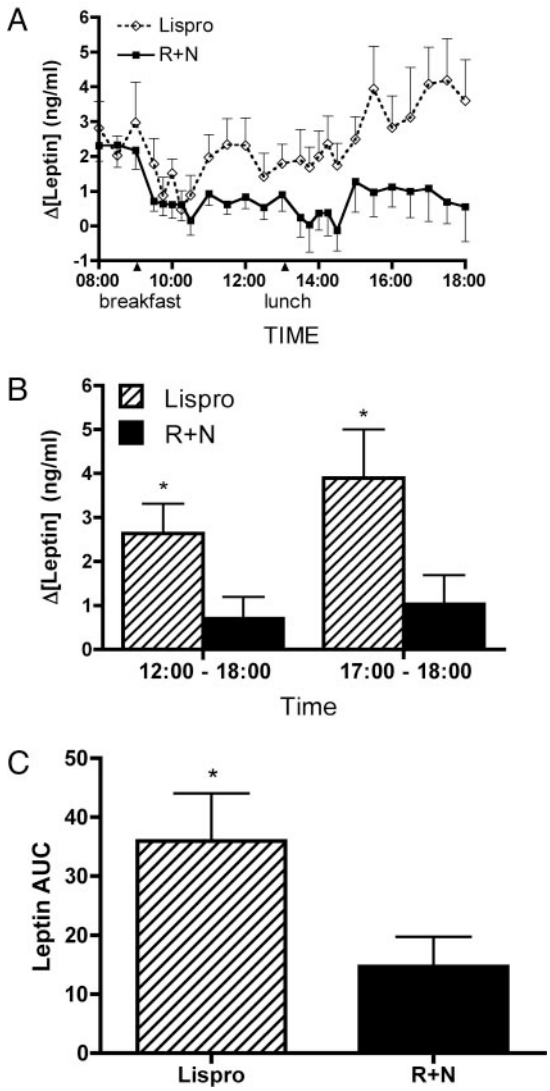

FIG. 3. A, The Δ[Leptin] concentrations over morning nadir levels over a 10-h period (0800–1800 h) in 10 female subjects with T1DM receiving Lispro insulin or R+N. B, The Δ[Leptin] concentrations over morning nadir levels during the periods from 1200 to 1800 h and from 1700 to 1800 h in 10 female subjects with T1DM receiving Lispro insulin or R+N. *, $P < 0.05$ for Lispro treatment, compared with R+N. C, The AUC for plasma leptin concentrations above morning nadir levels over 10 h in 10 female subjects with T1DM receiving Lispro insulin or R+N. *, $P = 0.003$ for Lispro treatment, compared with R+N.

insulin patterns and glucose disposal were most apparent, the mean Δ[Leptin] did not significantly change from nadir in the R+N treatment for either the 1200–1800 h time period (0.7 ± 0.5; ns) or the final hour of observation (1700–1800 h time interval, 1.0 ± 0.7; ns; Fig. 3B). However, a very significant increase in leptin was observed on the Lispro treatment day during both time periods (2.6 ± 0.7 for the 1200–1800 h time interval; $P < 0.0025$; and 3.9 ± 1.0 for the 1700–1800 h time interval; $P < 0.0025$). The mean Δ[Leptin] on the Lispro day was also significantly higher than on the R+N treatment day during both the 1200–1800 h interval ($P = 0.024$) and during the 1700–1800 h interval ($P = 0.026$; Fig. 3B). Similarly, the total leptin AUC (above morning nadir levels) over the entire 10-h period was more than two times larger on the Lispro treatment day (33.6 ± 5.7 ng/ml per 10 h) than on the R+N treatment day (14.7 ± 5.0 ng/ml per 10 h; $P = 0.003$ *vs.* Lispro) (Fig. 3C). Postprandial leptin responses and the AUC on the Lispro treatment day were similar to those observed over this same 10-h period in nondiabetic women with normal endogenous insulin secretion (35.5 ± 4.9 ng/ml per 10 h (21).

Ghrelin

Baseline fasting plasma ghrelin concentrations (mean of 0800, 0830, and 0900 h samples) in these females with T1DM were not different between Lispro (183.0 ± 25.9 pg/ml) and R+N (202.6 ± 37.3 pg/ml) treatment days. Ghrelin concentrations decreased 1–3 h after breakfast on both insulin regimens and then rose gradually until lunch (Fig. 4A), similar to reports in nondiabetic individuals (22). Postprandial suppression of ghrelin after breakfast tended to be greater on the Lispro than the R+N day, but this difference did not achieve statistical significance ($P = 0.119$). In contrast, the suppression of ghrelin after lunch was significantly more pronounced at 30 ($P = 0.004$), 75 ($P = 0.006$), 90 ($P = 0.002$), and 120 min ($P = 0.05$) when the subjects received Lispro insulin with lunch, compared with the conventional R+N treatment. On the Lispro treatment day, the suppression of ghrelin was apparent 30 min after lunch and was sustained significantly longer, taking an average of 169 min to return to prelunch levels, compared with 52 min with R+N treatment ($P = 0.008$). Whereas the 10-h AUC for plasma ghrelin concentrations was not significantly different on the 2 treatment days, the decrease of plasma ghrelin levels during the 2.5-h period after lunch was significantly different, with the 2.5-h

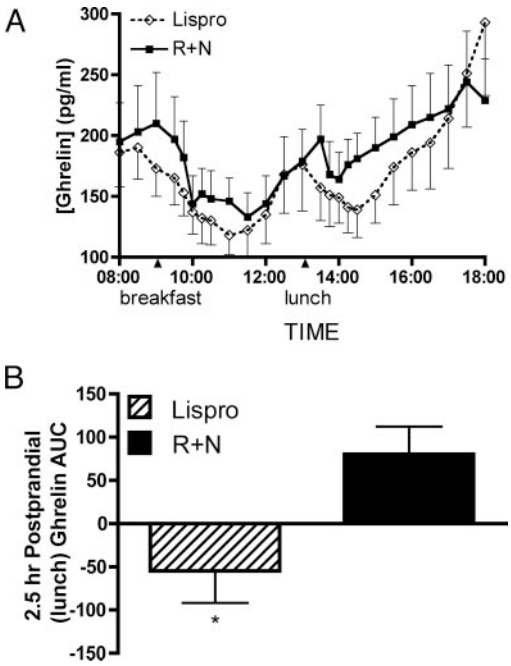

FIG. 4. A, Plasma ghrelin concentrations over a 10-h period (0800–1800 h) in 10 female subjects with T1DM receiving Lispro insulin or R+N. B, The AUC for plasma ghrelin concentrations from prelunch levels during the 2.5-h period after lunch in 10 female subjects with T1DM receiving Lispro insulin or R+N. *, $P < 0.01$ for Lispro treatment, compared with R+N.

AUC being positive on the R+N day and negative on the Lispro day ($P = 0.008$; Fig. 4B).

Discussion

There is evidence that insulin-stimulated glucose disposal is involved in the postprandial regulation of both leptin and ghrelin. Recent advances in insulin therapy, including rapid-acting insulin analogs, allow patients with diabetes to more closely match the kinetics of normal, endogenously secreted insulin. More physiological insulin responses to meals result in improved glucose disposal and may normalize the regulation of hormones involved in the control of energy homeostasis. We hypothesized that patients with T1DM treated at mealtime with rapid-acting Lispro insulin would have increased leptin production and a greater suppression of ghrelin in the postprandial period, compared with a more conventional R+N treatment.

As expected, administration of Lispro insulin with breakfast and lunch resulted in two rapid-onset peaks in circulating insulin concentrations, whereas a single injection of R+N produced a single peak of slower onset and more sustained duration. Although total insulin exposure over the course of the day did not differ between the two insulin treatments, Lispro treatment substantially improved glycemic control, as in previous reports (23, 24). This observation is consistent with the importance of early insulin secretion in the control of meal-induced glucose excursion and day-long glycemia (25).

In nondiabetic subjects, circulating leptin concentrations exhibit a diurnal pattern with a nadir in the midmorning and a late-night nocturnal peak (11, 21). The diurnal leptin pattern is dependent on insulin responses to meals and is therefore influenced by meal timing (21) and dietary macronutrient composition (8). Meal-induced insulin secretion increases plasma leptin concentrations within 3–6 h (21). Insulin plays a major role in the regulation of leptin production, stimulating the transcriptional activity of the leptin promoter, increasing leptin gene expression and elevating circulating leptin concentrations. These effects are all mediated by insulin's actions to promote glucose uptake and oxidative metabolism in adipocytes (26–28). Thus, improved glycemic control is expected to result in increased glucose use by adipose tissue, enhance leptin production, and potentially improve body weight regulation.

On the day that Lispro was administered, the rise of leptin was three to four times larger and the leptin AUC was increased by 2.5 times, compared with a single morning injection of R+N. This difference was observed despite similar overall insulin exposure and intake of identical meals on the 2 study days. These results suggest that administration of Lispro insulin with meals enhances postprandial glucose use in adipose tissue, leading to increased leptin production. Improved leptin production augments the amplitude of the diurnal pattern of circulating leptin levels, which has been implicated as a signal in the long-term regulation of energy balance and body adiposity (29).

In nondiabetic individuals, plasma ghrelin concentrations increase before meals and decrease after meals (22), Administration of exogenous ghrelin enhances appetite and increases food intake in humans (15) and decreases fat use, resulting in weight gain in rodents (30). Postprandial suppression of ghrelin is apparent within 30 min and reaches the nadir 1–2 h after a meal (31). There is evidence, consistent with the results of this study, that insulin is involved in the postprandial suppression of ghrelin (32–34). Circulating ghrelin concentrations are increased in the presence of hyperglycemia in streptozotocin-induced diabetic rats (35) as well as humans with T1DM (33). Insulin treatment in rats with streptozotocin-induced diabetes significantly reduces ghrelin levels (35). Correction of insulin deficiency in individuals with T1DM also inhibits ghrelin, whereas insulin deficiency results in a lack of postprandial suppression of ghrelin (33). Indeed, increased ghrelin signaling in T1DM has been implicated as a contributing factor in the pathogenesis of diabetic hyperphagia (36). Ghrelin levels may also respond to changes in body weight via changes in insulin levels associated with body adiposity (37). Thus, dysregulation of ghrelin appears to be a potential contributing factor to the overrepresentation of overweight and obesity in T1DM.

As expected, plasma ghrelin levels decreased after breakfast in these T1DM subjects when they were treated with insulin at the onset of the meal. However, the postprandial suppression after lunch was significantly more pronounced after the short-acting Lispro insulin with lunch than on the day the subjects received R+N administered only at breakfast. Given the similar degree of overall insulin exposure and nutrient ingestion, yet the clearly different levels of glucose disposal and use, these results suggest that the decrease in ghrelin levels in response to insulin is mediated, at least in part, by insulin effects on cellular glucose uptake and/or metabolism as opposed to an effect of insulin *per se*.

Differentiating the effects of glucose from insulin on ghrelin secretion, as well as leptin production, has been challenging. Many studies have used the glycemic clamp, during which insulin and glucose are simultaneously administered iv. Flanagan *et al.* (32) reported a decrease in circulating ghrelin after administration of insulin and glucose, and the authors suggest that insulin may inhibit ghrelin secretion, independently of glucose. Because insulin and glucose were administered together, however, it is not possible to determine whether the observed suppression of ghrelin secretion was due to direct effects of insulin or its effects on glucose metabolism. In healthy subjects, coinfusion of supraphysiological levels of insulin with glucose decreased plasma ghrelin concentrations by approximately 50% below baseline levels, whereas infusion of glucose without insulin, resulting in elevated plasma glucose levels and increased endogenous insulin secretion, did not decrease ghrelin concentrations (38). Because ghrelin was not measured until thirty min after infusion, early suppression of ghrelin in these insulin-sensitive individuals may have been missed.

In contrast, a recent study in obese individuals using hyperinsulinemic euglycemic clamps demonstrated that insulin infusion acutely decreases plasma ghrelin levels in obese subjects (39). The degree of suppression of ghrelin was related to insulin-mediated glucose use. These data support the hypothesis that insulin regulates ghrelin secretion via its effects on glucose uptake and metabolism, similar to the manner in which insulin regulates leptin production (26). In

the present study, overall insulin exposure and nutrient ingestion were similar on both treatment days; however, glucose disposal, the stimulation of leptin, and the postprandial suppression of ghrelin were all substantially greater on the day the subjects received Lispro insulin.

Conclusions

Leptin and ghrelin have major roles in the regulation of energy balance and fuel use (8), and normal regulation of these hormones is required to maintain energy homeostasis in humans (9, 10). Insulin exerts direct central nervous system effects on energy metabolism and regulates circulating leptin and ghrelin concentrations. The results of the present study support the hypothesis that insulin's effects to increase leptin production and suppress ghrelin secretion are, at least in part, meditated by enhanced glucose uptake and metabolism in response to insulin. Rapid-acting Lispro insulin administered with meals, compared with more conventional R+N regimens, increase leptin production and enhance postprandial suppression of ghrelin. Although this study did not profile 24-h leptin and ghrelin, the patterns of daytime leptin and ghrelin on the Lispro treatment day were much more similar to those previously reported in nondiabetic individuals (21, 31, 40). It remains to be determined in long-term studies whether insulin regimens that improve postprandial glycemic control, and normalize the regulation of leptin and ghrelin, will ultimately provide better long-term control of body weight/adiposity in patients with T1DM.

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